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Subject: Clinical Review of BLA Supplement 103780 / 5010
Serono, Inc.; Rebif

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To: STN# 103780 / 5010 File

This document is the Medical Officer's Clinical Review for STN# 103780 / 5010

Sponsor:	Serono, Inc.
Product:	Rebif
Indication:	Treatment of multiple sclerosis
Regimen:	44 micrograms subcutaneous three times per week
Purpose of supplement:	To revise the package insert based on the 48-week results from study 21125

Dates of Submissions:

Supplement 103780 / 5010 submitted on June 28, 2002, received on July 2, 2002

Supplemental Information:

June 28, 2002	–	Case Report Forms
July 24, 2002	–	Revised Electronic Submission
February 28, 2003	–	Revised Package Insert
April 1, 2003	–	Responses to CBER Questions Regarding Efficacy Analyses, Neutralizing Antibodies, and Protocol Compliance
April 8, 2003	–	Responses to CBER Questions Regarding Protocol Deviations
April 15, 2003	–	Financial Disclosure

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OVERVIEW

Interferon ß -1a (Rebif®) is marketed (U.S. License number 1574) by Serono, Inc. for the treatment of patients with relapsing forms of multiple sclerosis (MS). Marketing approval was granted on 3/7/2002 based primarily on the results of two randomized controlled clinical trials. The first of these trials was a randomized, double-blind, placebo-controlled 560-subject study of 22 µg *vs.* 44 µg Rebif® *vs.* placebo administered subcutaneously (SC) three times per week for 2 years. Based on the review of the BLA submission of February 27, 1998, CBER concluded that both doses of Rebif® were demonstrated to be safe and effective and to be approvable for treatment of relapsing-remitting multiple sclerosis (RRMS). However, due to the orphan drug exclusivity of Avonex® (another interferon ß-1a; Biogen) and Betaseron® (an interferon ß-1b; Chiron), Rebif® was not approved. In order to break orphan exclusivity, Serono initiated a superiority study to demonstrate an advantage of Rebif® over Avonex®. This second study was a randomized, open-label study in which subjects with RRMS were treated with either Rebif® 44 µg SC three times per week or Avonex® 30 µg IM once weekly. Although the duration of the study was 48 weeks, the pre-specified primary outcome measure was the proportion of subjects who remained relapse-free following 24 weeks of treatment. Based on the complete results of the initial 24 weeks of this comparative study, as well as summary data from 48 weeks, CBER concluded that Rebif® demonstrated a superior clinical benefit over Avonex®, allowing Serono to break Biogen's orphan drug exclusivity and thus, to market Rebif® in the U.S. for the treatment of relapsing-remitting MS. To review the rationale behind the process of breaking Axonex®'s orphan exclusivity, see the discussions by Drs. C. Rask, E. Unger, M. Walton, and M. Haffner (http://www.fda.gov/cber/review/ifnbser030702r1.pdf and http://www.fda.gov/cber/review/ifnbser030702r2.pdf). However, the full 48-week final study report of the comparative trial was not submitted until June 28, 2002. The final 48-week data are the subject of this review.

Scope of this review

The focus of this document is upon safety and efficacy data from a single study, 21125, a randomized, open-label comparative study of the use of Rebif® 44 µg administered SC 3x per week *vs.* Avonex® 30 µg administered IM once weekly. Emphasis is placed on the results of the second 24 weeks of the study, particularly the extent to which the results of the second half of the study support or fail to support the previous conclusions based on the first 24 weeks of the study.

The review contains two separate sections to evaluate the study's efficacy results. The first emphasizes the study results over the entire course of the study, from Weeks 0 to 48. The objective of this section is to consider the extent to which the full 48-week results confirm the findings seen at 24-weeks. The second section emphasizes the study results over Weeks 24 – 48. The objective of this second efficacy section is to consider whether there is any benefit of one agent over the other during the second 24 weeks, particularly to consider whether the benefit seen at 24-weeks increases, decreases, or is stable. For more complete background and study design information, including a detailed analysis of the 24-week results, see Dr. Cynthia Rask's review of this BLA supplement (http://www.fda.gov/cber/review/ifnbser030702r3.pdf).

Abbreviations and Definitions of Terms Used in This Review

ADL	Activities of Daily Living
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
Avonex®	Biogen's recombinant human interferon β-1a
Betaseron®	Berlex's recombinant human interferon β-1b
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CU	Combined Unique (T1 + T2)
EDSS	(Kurtzke's) Expanded Disability Status Scale
IFN	Interferon
IFN β-1a	Recombinant human interferon β-1a
IM	Intramuscular (ly)
ITT	Intent-to-treat
KFS	Kurtzke Functional Systems
LU	Laboratory units
mcg	microgram
mL	milliliter
MIU	Million International Units (10^6 IU)
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NAb	Neutralizing antibody(ies)
NOS	Not otherwise specified
NU	Neutralizing units
Rebif®	Serono's recombinant human interferon β-1a
RES	Reticuloendothelial system
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious Adverse Event
SC	Subcutaneous (ly)
SGOT (AST)	Serum glutamic oxaloacetic transaminase
SGPT (ALT)	Serum glutamic pyruvic transaminase
SPMS	Secondary progressive multiple sclerosis
T1	T1-weighted MRI scanning sequence
T2	T2-weighted MRI scanning sequence
tiw	three times per week
µg	microgram(s)

INTRODUCTION

MULTIPLE SCLEROSIS

Background

Multiple Sclerosis (MS) is a chronic, inflammatory, possibly autoimmune, demyelinating disease of the central nervous system. MS is a common cause of neurological disability in young adults, primarily affecting people between 20 and 40 years of age, and affecting women approximately twice as often as men. Experts in the field generally recognize three clinical forms of MS: relapsing-remitting, secondary progressive and primary progressive (Lublin and Reingold, 1996). Relapsing-remitting MS (RRMS) is the presenting form in up to an estimated 80-85% of subjects, and involves recurrent attacks of neurological symptoms and signs (relapses or exacerbations) involving multiple areas of the nervous system that occur at variable time intervals ranging from months to years between attacks. These exacerbations or relapses are followed by variable degrees of recovery (remissions). The majority of subjects with RRMS develop secondary progressive MS (SPMS) in which periods of stable recovery give way to neurological decline over time. About 50% of subjects with RRMS will develop SPMS within 10 years of onset; the proportion approaches 80% after 25 years (Runmarker and Anderson, 1993).

Current Treatment of MS

There are currently five drugs approved in the United States for treatment of MS. Betaseron® (Interferon β-1b), Avonex® (Interferon β-1a), Rebif® (Interferon ß-1a), and Copaxone® (glatiramer acetate – formerly known as copolymer-1) are licensed for the treatment of relapsing-remitting MS (Copaxone®) or relapsing forms of MS (Betaseron®, Avonex®, and Rebif®). Novantrone® (Mitoxantrone), a cancer chemotherapeutic agent, was approved in 2000 for patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis.

PROTOCOL 21125

Title: An Open-Label, Randomized, Multicenter, Comparative, Parallel Group Study of Rebif® 44 µg Administered Three Times per Week by Subcutaneous Injection, Compared with Avonex® 30 µg Administered Once per Week by Intramuscular Injection in the Treatment of Relapsing-Remitting Multiple Sclerosis

Period of Study Conduct: November 1999 to August 2001

Funding: Serono, Inc.

Objectives

The primary objective was to demonstrate that the proportion of patients with relapsing-remitting MS who were exacerbation-free would be greater with Rebif® 44 µg administered

three times per week (132 µg per week) than with Avonex® 30 µg administered once per week for 24 weeks.

The principal secondary objective as stated in the protocol was that the combined unique (CU) lesion activity, as determined by magnetic resonance imaging (MRI), would be less after 24 weeks of treatment with Rebif® 44 µg three times per week than with Avonex® 30 µg once per week.

The objectives of the second 24 weeks of the study were to assess the durability of the results of the first 24 weeks of the study and to provide more meaningful data regarding disease progression and immunogenicity.

Design

This was a multicenter, open-label, randomized, comparative, parallel group study in which up to 624 interferon-naïve subjects with RRMS were randomized equally to receive either Rebif® 44 µg administered SC three times per week or Avonex® 30 µg administered IM once per week for 48 weeks. Although all enrolled subjects were to complete 48 weeks of treatment, the efficacy outcomes were to be determined after 24 weeks of treatment. The primary study endpoint was the proportion of subjects who were exacerbation-free at 24 weeks.

T2-weighted and T1-weighted pre- and post gadolinium enhanced MRIs were obtained within 28 ± 4 days of beginning treatment and monthly thereafter until Week 24. The only scheduled MRIs after Week 24 were T2-weighted and T1-weighted images, ---------- gadolinium, at Week 48 (or study termination). Blinded evaluators at the University of British Columbia, Vancouver, BC interpreted all pre- and post-treatment MRIs.

Each center was required to have two separate physicians responsible for the management of each subject: a treating physician and an evaluating physician. The treating physician was responsible for the supervision of study drug administration, for reporting and treating adverse events and monitoring safety assessments. The treating physician was also responsible for the treatment of exacerbations and for determining whether non-MS-related factors could account for neurological worsening. The evaluating physician was to remain unaware of treatment assignments, adverse event profiles, and any changes in safety assessments throughout the trial. The evaluating physician was to determine whether or not an exacerbation meeting the protocol's definition had occurred, and would evaluate its severity based on changes in the Expanded Disability Status Scale (EDSS) and the Kurtzke Functional Systems (KFS) score.

Material Source

Rebif® was supplied as a sterile solution in pre-filled syringes for subcutaneous administration. Each syringe contained 0.5 mL of solution, which contained 44 µg (12 MIU) of interferon β-1a. The study material was identical to commercially available Rebif®.

Commercially available Avonex® 30 µg for IM administration was reconstituted and administered according to the directions in the package insert.

Randomization

Subjects who completed screening procedures and were found to be eligible for the study were to be enrolled and randomized (stratified by center) within 24 hours of the completion of screening.

Inclusion Criteria

Subjects were deemed eligible for participation in the study if they met the following criteria (abbreviated list):

- Age between 18 and 55 years
- Clinically definite or laboratory-supported diagnosis of relapsing-remitting MS, according to Poser's criteria
- Two or more relapses within the preceding 24 months
- Clinical stability or improving neurological state during the four weeks prior to Study Day 1
- Expanded Disability Status Scale (EDSS) score of 0 to 5.5, inclusive
- Two or more lesions consistent with MS on a screening T2-weighted MRI performed within 28 ± 4 days of Study Day 1

Exclusion Criteria

Subjects were to be excluded if any of the following were present (abbreviated list):

- Secondary progressive, primary progressive or progressive relapsing MS
- Prior use of interferon
- Treatment with oral or systemic corticosteroids or ACTH within 4 weeks of Study Day 1 or 7 days of the screening MRI

Treatment

Dose and Administration

Subjects enrolled in this study were to receive one of two treatments for a period of at least 48 weeks:

- Rebif® 44 µg, administered SC three times weekly, or
- Avonex® 30 µg, administered IM once weekly

Dose Titration

In order to minimize potential side effects at the beginning of treatment with Rebif®, a dose titration schedule was instituted. The dose administered was gradually increased over the first four weeks of treatment, with 8.8 µg 3 times per week (20% of total) for the first two weeks, 22 µg 3 times per week (50% of total) for the third and fourth weeks, and the full dose of 44 µg 3 times per week for the duration of the study.

The Avonex® dose was not titrated, and was administered at 30 µg once per week beginning at Study Day 1 and continued throughout the study.

Evaluations Performed During the Study

The study flowchart is shown in Table 1.

Table 1: Study Procedures

Procedure	28 ± 4 Days Prior to Day 1	7 Days Prior to Day 1	Day 1	Week 4	Week 8	Week 12	Weeks 16 and 20	Week 24	Week 36	Week 48 and Termination Visit
Medical History	X									
Physical Examination*	X		X			X		X	X	X
Minor Office Visit				X	X		X			
Neurological Examination**	X		X			X		X	X	X
MRI	X		X	X	X	X	X	X		X****
Labs***		X		X		X		X	X	X
Thyroid Function Tests		X						X		X
Antibodies to IFN-b		X						X		X
Document Exacerbations	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X

*after screening, includes only weight and vital signs
** includes the EDSS, KFS, Distance Walked, and Timed Ambulation Index
*** includes hematology, blood chemistries, urinalysis
****MRIs ---------- gadolinium

Neurological Examinations

Measures were undertaken to keep the examining physician, who was to perform all neurological examinations, blinded to treatment assignment. To mask injection site reactions, subjects were instructed to cover injection sites prior to neurological examinations. Neurological examinations included evaluations of the EDSS, KFS scores, ambulation up to 500 meters, and timed ambulation. All neurological examinations were to be performed without consulting a subject's previous neurological examination.

When neurological examinations and MRI scans were scheduled for the same visit, they were to be performed on the same day whenever possible; otherwise, a time difference of no more than ± 48 hours between the evaluations was permissible.

Evaluation of Exacerbations During the Study
An exacerbation was defined as the appearance of a new symptom or worsening of an old symptom attributable to MS, accompanied by an appropriate new neurological abnormality or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days. Subjects were instructed to inform the study center within 48 hours of the onset of an exacerbation, and at that time the treating physician or designate would discuss the symptoms with the subject and determine whether a neurological examination was indicated. If so, the subject would be advised to go to the center for evaluation. The evaluating physician was to determine whether or not an exacerbation meeting the protocol's definition had occurred and would evaluate its severity based on changes in the EDSS and the Kurtzke Functional Systems (KFS) score, as follows:

- Mild: EDSS change of 0 to 0.5 point, with a new neurological finding and/or and increase in KFS score of one point in one to three systems
- Moderate: EDSS change of 1.0 to 2.0 points and/or an increase in KFS score of one point in four or more systems or of two points in one to three systems
- Severe: EDSS and/or KFS score increases that exceed those described for a moderate exacerbation

The treating physician or designate would conduct weekly phone checks to determine when the exacerbation reached maximum severity and began to improve. If necessary, the subject would undergo further neurological examinations; exacerbation severity would be graded according to the worst EDSS and KFS scores recorded during the exacerbation.

Subject Contacts Between Scheduled Visits
These contacts were to have occurred by telephone at Weeks 2, 6, 10, 14, 18, 22, and every 4 weeks from Week 24 to Week 48 to determine whether any symptoms consistent with an exacerbation had occurred, and whether or not an unscheduled neurological examination by the evaluating physician was needed.

Unscheduled Visits
Subjects could be seen at any time during the study for evaluation of a possible MS exacerbation or for evaluation of possible adverse events.

Assessment of T2 Activity
A T2 active lesion was defined as any new, recurrent, newly enlarging, or persistently enlarging T2 lesion; a T2 active scan was defined as a scan showing any T2 active lesions.

Assessment of T1 Activity
A T1 active lesion was defined as any newly enhancing, recurrent enhancing or persistently enhancing T1 lesion; a T1 active scan was defined as a scan showing any T1 active lesions.

Assessment of Combined Unique Activity
A combined unique (CU) active lesion was defined as any lesion that was T1 active, T2 active or both; a CU active scan was defined as a scan showing any CU active lesions.

Determination of Antibodies to Interferon-b
Sera were tested for antibodies to interferon-β prior to the first administration of study drug. At 24 and 48 weeks, sera were tested at least 24 hours after the administration of study drug. Baseline or Week 24 samples positive for ---------- were tested for neutralizing antibody (NAb). Week 48 samples were tested for both ---------- and NAb. Assays for NAb were performed on all samples at the same time, after all Week 48 samples were available. Assays were performed at a central laboratory.

Efficacy Endpoints

Primary Endpoint
Proportion of subjects who were exacerbation-free after 24 weeks; the same outcome was the primary clinical endpoint at Week 48.

Secondary Endpoints
As ranked in order of importance prospectively by the Applicant:

1. The mean number of CU active lesions per subject per scan (Week 24 only)
2. The total exacerbation count per subject (Weeks 24 and 48)
3. The mean number of T2 active lesions per subject per scan (Weeks 24 and 48)

Tertiary Endpoints
- MRI measures
  - Proportion of CU active scans per patient; proportion of subjects with no CU active lesions (Week 24 only)
  - Proportion of T2 active scans per patient; proportion of subjects with no T2 active lesions (Weeks 24 and 48)
  - Proportion of T1 active scans per patient; proportion of subjects with no T1 active lesions (Weeks 24 and 48)
- Relapse measures
  - Time to first relapse (Weeks 24 and 48)
  - Time to second relapse (Week 48 only)
  - Relapse severity (Weeks 24 and 48)
- Progression measures
  - Change in EDSS (Week 48 only)
  - Time to disability progression confirmed at 3 and 6 months (Week 48 only)
- NAb measures
  - Proportion of subjects developing NAb (Weeks 24 and 48, both reported only in current supplement)
  - Effect of NAb development on proportion relapse-free, relapse count, and T2 active lesion count (Weeks 24 and 48, both reported only in current supplement)

Safety Endpoints

Safety Measurements Analyzed
The following safety parameters were to be analyzed in detail, in addition to the usual more general safety analyses:

- Incidence of development of thyroid function test abnormalities, including T3, T4, and TSH; thyroperoxidase antibody if T3, T4, or TSH was abnormal
- Incidence of development of antibodies to interferon-β

Statistical Analysis Plan

Study Day 1 was considered to be the first day when study drug was administered.

The endpoints (primary, secondary and tertiary) were all pre-specified in the protocol and in the statistical analysis plan submitted to the FDA prior to the analysis of the study results. All analyses were conducted using two-sided tests of significance, and no adjustment was made for multiplicity, as agreed with FDA in October 2000.

Determination of Sample Size
It was estimated that a sample size of 280 evaluable subjects per treatment group would provide 95% power to detect a 30% difference in the primary endpoint, the proportion of subjects exacerbation-free at 24 weeks in the Rebif® group compared to the Avonex® group. Assuming a 10% dropout/non-evaluable rate, 312 subjects per group or 624 total subjects were to be randomized. No interim analyses were planned or conducted between Weeks 0 and 24 or between Weeks 24 and 48.

Analysis Populations
Baseline and efficacy data were to be analyzed for two subject populations: the Intent-to-Treat (ITT) Population and the Evaluable Population.

The ITT Population for the primary efficacy parameter was to include all randomized subjects. Because two centers (Centers 267 and 291) chose *a priori* not to perform MRIs on their subjects, the subjects from those two centers were excluded from the ITT efficacy population for the MRI parameters.

The Evaluable Population was to include those subjects who had no major protocol deviations and who had either completed 48 weeks of treatment or satisfied criteria specific to individual endpoints:

- For the primary endpoint (proportion of subjects exacerbation-free at 48 weeks), a subject who stopped treatment before 48 weeks would be included in the Evaluable Population if he/she had experienced an exacerbation while on treatment.
- For MRI parameters, a subject who stopped treatment before 48 weeks would be included in the Evaluable Population if he/she had had at least one post-baseline MRI scan while on treatment. Only MRI scans obtained during treatment were included in the analysis of such subjects.

- For the total exacerbation count at 48 weeks, all subjects who stopped treatment before 48 weeks would be included in the Evaluable Population; however, only exacerbations occurring during treatment would be included in the analysis.

The ITT Population was agreed to be the primary analysis population for all clinical and MRI outcomes in the Statistical Analysis Plan.

Significance Testing, Allocation of Alpha
A Type I error rate of 0.05 was used for the analysis of the primary endpoint at 24 weeks. The 48-week data is used for confirmatory and exploratory analyses. No alpha was allocated to the analysis of endpoints at 48 weeks.

Analysis of Baseline Parameters
Baseline data were defined as the last data collected before the first injection of Rebif® or Avonex®, either on Study Day 1 or as shortly as possible before Study Day 1.

Continuous baseline parameters were to be analyzed using a two-way analysis of variance (ANOVA) model on the ranked data, with effects for treatment and center. The full analysis model using ranked data, including the main effects and treatment-by-center interaction, was to be used to test for a significant interaction. If the interaction was significant, the full model would be considered the final model. It was not expected that ANOVA model assumptions would be satisfied, but if they were, the raw data would be used in the model as the definitive analysis.

Nominal-scaled categorical baseline parameters were to be analyzed using the Cochran-Mantel-Haenszel (CMH) general association test, and the row means score test would be used for ordinal-scaled categorical parameters. Both analyses would be adjusted for center.

If the treatment groups differed statistically in any baseline parameter, the efficacy analyses would be adjusted for this imbalance. If any baseline parameters were thought to be clinically different between the treatment groups, the analyses of these parameters would also be adjusted for the imbalances as supportive analyses.

Primary Endpoint – Proportion of Subjects Exacerbation-Free

The primary statistical analysis was performed on the 24-week data.

For the current 48-week report, the primary efficacy endpoint, proportion of exacerbation-free subjects at 48 weeks, was to be analyzed using a logistic regression model. The results were to be expressed as an odds ratio, adjusted for center and treatment effects, using Avonex® as the comparator.

Handling of Drop-Outs or Missing Data
For subjects who withdrew from the study before Week 48 without an exacerbation (i.e., did not receive 48 weeks of treatment and were not followed up for 48 weeks), the proportion that would be considered to be exacerbation-free was estimated as follows:

- The number of subjects in each treatment group who withdrew without an exacerbation was determined.
- The proportion of exacerbation-free subjects among those with known status was determined across both treatment groups (i.e., the number of subjects exacerbation-free at 48 weeks divided by the total number of subjects exacerbation-free at 48 weeks and the number of subjects who had an exacerbation at any time during the study).
- For subjects withdrawing without an exacerbation in each treatment group, the number who would be considered exacerbation-free was determined as the product of these two numbers (the total number of subjects in the treatment group withdrawing without an exacerbation and the overall proportion of exacerbation-free subjects). These estimates were rounded up to the next integer if the decimal part was ≥ 0.5 and rounded down otherwise.

Secondary Endpoint – Clinical Analytic Methods
Exacerbation count was to be analyzed using a Poisson regression model with factors for treatment and center.

Secondary Endpoints – MRI Analytic Methods

The main secondary efficacy endpoint was the mean number of CU active lesions per subject per scan during 24 weeks of treatment. It was to be analyzed using a nonparametric ANCOVA model with effects for treatment and center, with the baseline number of CU active lesions as the single covariate in the model.

All additional MRI parameters, with the exception of the three different proportions of subjects with no active MRI lesions, were to be analyzed using a nonparametric analysis of covariance (ANCOVA) model with effects for treatment and center, with the corresponding baseline number of active lesions as the single covariate.

The analysis plan, including the approaches to missing clinical and MRI data, was identical to the analysis plan for the 24-week data. For details of the analysis plan, see the review by Dr. C. Rask (http://www.fda.gov/cber/review/ifnbser030702r3.pdf).

Safety Analyses

All subjects who received at least one injection of Rebif® or Avonex® are included, as treated, in the safety analyses.

STUDY ADMINISTRATION

The study administration during weeks 24 – 48 was the same as the study administration during the initial 24 weeks of the study.

DIFFERENCES IN STUDY DESIGN, WEEKS 0-24 VS. WEEKS 24-48

Study monitoring differed during the two portions of the study. These differences limit the interpretability of analyses comparing Weeks 0-24 to Weeks 24-48. Major differences in study monitoring include the following:

- During Weeks 0-24, T1 and T2 MRI scans, ---------- gadolinium, were performed every 4 weeks, allowing a determination of combined unique (CU) lesions as a secondary endpoint. After the Week 24 MRI scan, the only MRI scan was a single T2 scan, ---------- gadolinium, at Week 48. Therefore, the Week 24-48 data do not include the number of CU lesions but use instead the mean number of T2 lesions per subject per scan as a secondary endpoint.

- During Weeks 0-24, scheduled minor office visits or neurological examination visits occurred every 4 weeks, with telephone contacts every two weeks between office visits. During Weeks 24-48, scheduled neurological examination visits occurred only twice, at weeks 36 and 48, with telephone contacts every 4 weeks between office visits.

Reviewer's comment: By design, therefore, there was greater potential to fail to capture very mild exacerbations during the second part of the study, relative to the first part of the study.

The study endpoints also differed between the two portions of the study.

- Endpoints related to MRI CU lesions, including the following, were assessed at 24 weeks but not at 48 weeks:

  - mean number of CU active lesions per subject per scan (secondary endpoint);
  - proportion of CU active scans per patient (tertiary endpoint);
  - proportion of subjects with no CU active lesions (tertiary endpoint).

Several tertiary endpoints related to disability progression or the occurrence of a second relapse, including the following, were assessed at 48 weeks but not at 24 weeks:

- Time to second relapse
- Change in EDSS
- Time to disability progression confirmed at 3 and 6 months

STUDY RESULTS

The study was conducted between November 1999 and August 2001.

FORMAL PROTOCOL MODIFICATIONS

The protocol dated August 13, 1999 was amended six times before August 7, 2001 (last subject, last 48 Week visit date). The initial 4 amendments were approved prior to the completion of the initial 24 weeks of the study. Amendments 5 and 6, summarized below, were approved after completion of the initial 24 weeks of the study:

- Amendment 5, dated March 29, 2001, provided for an extension to the treatment phase, added a ---------- use assessment, and added a clarification of the MRI requirements.
- Amendment 6, dated June 7, 2001, provided an option for treatment with Rebif® following Week 48 or termination, added an exclusion of Avonex® treatment in non-comparative phase of trial, added an option for Avonex® patients to transition to Rebif® or withdraw from study, removed the requirement for separate treating and evaluating physicians in non-comparative phase of trial, removed the requirement for patient contacts, and updated the ----------

CHANGES IN CONDUCT OF THE STUDY OR PLANNED ANALYSES

The following changes were made in the planned analyses (abbreviated list):

- Since only one hospitalization for an exacerbation occurred by 48 weeks other than for convenience of steroid administration, no analyses were performed for the parameter of hospitalizations for exacerbation.
- Site 238 experienced data fraud. An independent external audit advised exclusion of clinical and neurological data from this site. Full details of the relevant events and FDA assessment are included in the review of C. Rask (http://www.fda.gov/cber/review/ifnbser030702r3.pdf). Therefore, in addition to the planned analyses, statistical analyses for the primary and secondary outcome measures with the exclusion of this site were also performed for the primary and secondary clinical endpoints.

Protocol Deviations/Violations

Violations of Eligibility Criteria

Three subjects, all randomized to Avonex® treatment, failed to meet specific eligibility criteria. One subject did not have two or more lesions consistent with MS on a screening T2-weighted MRI performed within 28 ± 4 days of Study Day 1. One subject had previously used an interferon. One subject received treatment with oral or systemic corticosteroids or ACTH within 4 weeks of Study Day 1.

Violations that Occurred During the Conduct of the Study

During the complete 48 weeks of the study, the following 42 violations (20 in the Rebif® treatment group, 22 in the Avonex® treatment group) occurred in 36 subjects (17 in the Rebif® treatment group, 19 in the Avonex® treatment group) after randomization:

- 1 subject randomized to Rebif® and 2 randomized to Avonex® missed more than 25% of their prescribed study injections
- 10 subjects randomized to Rebif® and 17 subjects randomized to Avonex® received steroid treatment within 7 days prior to an MRI scan
- 4 subjects randomized to Rebif® used a prohibited medication during the study (concomitant medications for treatment of cancer, the other received steroids)
- 1 subject randomized to Rebif® and 1 subject randomized to Avonex® received corticosteroids for more than 30 consecutive days
- 4 subjects randomized to Rebif® and 2 subjects randomized to Avonex® became pregnant during the study

In addition, in response to requests from CBER, the Applicant assessed the impact of reversal of roles between treating and evaluating physicians:

- 29 subjects (4.3%) had reversal of roles between their treating and evaluating physicians: 11 randomized to Rebif® and 18 randomized to Avonex. Fifteen of these role reversals followed a pattern that is unlikely to affect the study outcome, such as the evaluating physician becoming the treating physician for the duration of the study, with a new evaluating physician for that subject. In fourteen of the role reversals (6 randomized to Rebif® and 8 randomized to Avonex), the unblinded treating physician became the evaluating physician, a reversal that could affect the study outcome. The effect of these role reversals is discussed in the "Exploratory Analyses" section of this review.

Number of Relapses Pre-Study

Sixteen subjects did not have 2 relapses within 2 years of study entry (5 in the Rebif® group, 11 in the Avonex® group). A detailed description and discussion of these cases is provided in the review by Dr. C. Rask (http://www.fda.gov/cber/review/ifnbser030702r3.pdf).

Study Conduct at Specific Study Sites

Significant irregularities occurred at a single site and were considered in both the 24-week and 48-week analyses. Three study sites were inspected prior to Rebif® licensure.

SUBJECT ENROLLMENT AND DISPOSITION

Fifty-six study sites (United States, Canada, and Europe) enrolled a total of 677 subjects. After randomization, 339 subjects were assigned to Rebif® 44 µg SC 3 x per week and 338 subjects were assigned to Avonex® 30 µg IM once per week.

Randomization

There were no errors in randomization. One subject randomized to Avonex® did not receive treatment. All 339 subjects randomized to Rebif® treatment received Rebif®.

Time on Study and on Treatment

Approximately 96% of subjects in both groups completed 48 weeks in the study. Subject enrollment and disposition are summarized in Table 2.

Three hundred fourteen subjects (92.6%) randomized to Rebif® completed 48 weeks of treatment. Of the 25 subjects who prematurely discontinued treatment, 11 (3.2%) continued in the study for 48 weeks.

Three hundred seventeen (93.8%) of the subjects randomized to Avonex® completed 48 weeks of treatment. Of the 21 who prematurely discontinued treatment, 7 (2.1%) continued in the study for 48 weeks.

Approximately 97% of subjects who completed 24 weeks of treatment also completed 48 weeks of treatment.

Reviewer's comment(s): There was excellent retention of subjects throughout the study. The high retention rate is essential to the validity and interpretability of the study results.

Table 2: Subject Disposition

	Rebif	Avonex
Screened but not randomized (n = 90)		
N randomized	339	338
Number who completed 48 weeks of study	325 (95.9%)	324 (95.9%)
Number who withdrew from study	14 (4.1%)	14 (4.1%)
Number who completed 48 weeks of treatment	314 (92.6%)	317 (93.8%)
Number who prematurely discontinued treatment	25 (7.4%)	21 (6.2%)
Adverse Event	14 (4.1%)	7 (2.1%)
Death	1 (0.3%)	0
Lack of Efficacy	3 (0.9%)	1 (0.3%)
Subject Decision	5 (1.5%)	9 (2.7%)
Pregnancy	2 (0.6%)	0
Lost to Follow-up	0	3 (0.9%)
Other	0	1* (0.3%)

* withdrew after randomization, but prior to initiation of treatment due to experiencing a relapse

Visit Schedule and Determination of Exacerbations During the Study
There were 326 unscheduled neurological examinations during the course of the study. Seventy-six of these were performed at an otherwise scheduled visit (at the "minor" office visits) and 247 at a completely unscheduled visit. Two hundred forty-four unscheduled visits occurred at which no neurological assessments were performed. These involved visits for repeat laboratory testing, adverse event assessments, follow-up of a prior relapse, termination of treatment, injection training, and for miscellaneous other reasons.

Subjects in the Avonex® group were seen more often for unscheduled visits than subjects in the Rebif® group and also had more unscheduled neurological assessments performed at scheduled visits (the "minor" office visits) during which a neurological assessment was not required by the protocol. In the Avonex® and Rebif® groups, the mean numbers of unscheduled visits per subject were 0.88 and 0.80, respectively.

Adherence to Protocol-Required Contacts Between Clinic Visits
For the subjects who completed the 48 weeks of the study, the mean portion of phone contacts that were completed were 85% for both treatment groups. For the 14 subjects randomized to Rebif® and the 13 subjects randomized to Avonex® who did not complete the 48 weeks of the study, the portion of the expected numbers of phone contacts that were completed were 65.8% and 80.9%, respectively.

Compliance

Treatment compliance throughout the study was excellent. Overall, subjects in each study group received 97% of their intended dose by volume. For all planned doses (not counting doses after treatment was discontinued) the numbers of doses reduced or omitted are shown in Table 3. The high compliance rate is essential to the interpretability of the study results.

Table 3: Compliance

Variable	Rebif, N = 339	Avonex N = 337
Volume Injected (% of planned volume)	97%	97%
Planned doses	46,903	15,808
Doses reduced	2047 (4.4%)	442 (2.8%)
Doses missed	740 (1.6%)	213 (1.3%)
Doses reduced or missed	2787 (5.9%)	655 (4.1%)

Adverse Events Leading to Premature Discontinuation

At 24 weeks, fourteen subjects were identified as discontinuing from the study due to adverse events. Eleven of these were in the Rebif® group (3.2% of the subjects randomized to Rebif®), and 3 were in the Avonex® group (0.9% of the subjects randomized to Avonex).

At 48 weeks, twenty-one subjects were identified as discontinuing from the study due to adverse events. Fourteen of these were in the Rebif® group (4.1% of the subjects randomized to Rebif®), and 7 were in the Avonex® group (2.1% of the subjects randomized to Avonex). The seven subjects who prematurely discontinued study participation between weeks 24 and 48 are shown in Table 4.

Table 4: Adverse Events Resulting in Premature Study Discontinuation, Weeks 24 - 48

Treatment Group	Subject ID	Adverse Event (s)
Rebif	1030015	Flu-like symptoms, increased depression, anxiety
	2970002	Increased headaches
	2970009	Increased fatigue, imbalance, intermittent headache, chemical hepatitis, generalized feelings of being unwell, increased baseline MS symptoms
Avonex	1030001	Increased fibromyalgia, intermittent fevers
	2340005	Vomiting
	2970006	Increased headaches, fatigue increased
	2970010	Arthralgias and myalgias on day following injection

Fourteen subjects were classified as prematurely discontinuing from the study primarily due to "patient decision." Nine of these 14 subjects also had ongoing adverse events at the time of study discontinuation, 2 in the Rebif® group, 5 in the Avonex® group. In addition, 2 of the 3 subjects classified as having prematurely discontinued from the study due to being "lost to follow-up" had ongoing adverse events at the time of study discontinuation. Both subjects were receiving Avonex®.

Demographics and Baseline Characteristics

Subjects had a mean age of 37.9 years and were predominantly white (91.0%) and female (74.7%). The treatment groups were well balanced with regard to demographics.

The treatment groups were also well balanced on baseline disease characteristics, including duration of disease, number of exacerbations in the previous one and two years, EDSS scores, and MRI characteristics.

For details of the demographics and baseline characteristics, see the review by Dr. C. Rask (http://www.fda.gov/cber/review/ifnbser030702r3.pdf).

EFFICACY RESULTS – WEEKS 0 TO 48

Primary Endpoint Results

During the 48-week treatment period, 61.7% of subjects in the Rebif® treatment group and 52.4% of subjects in the Avonex® treatment group remained exacerbation-free.

Table 5: Per Cent of Subjects with Exacerbations and without Exacerbations

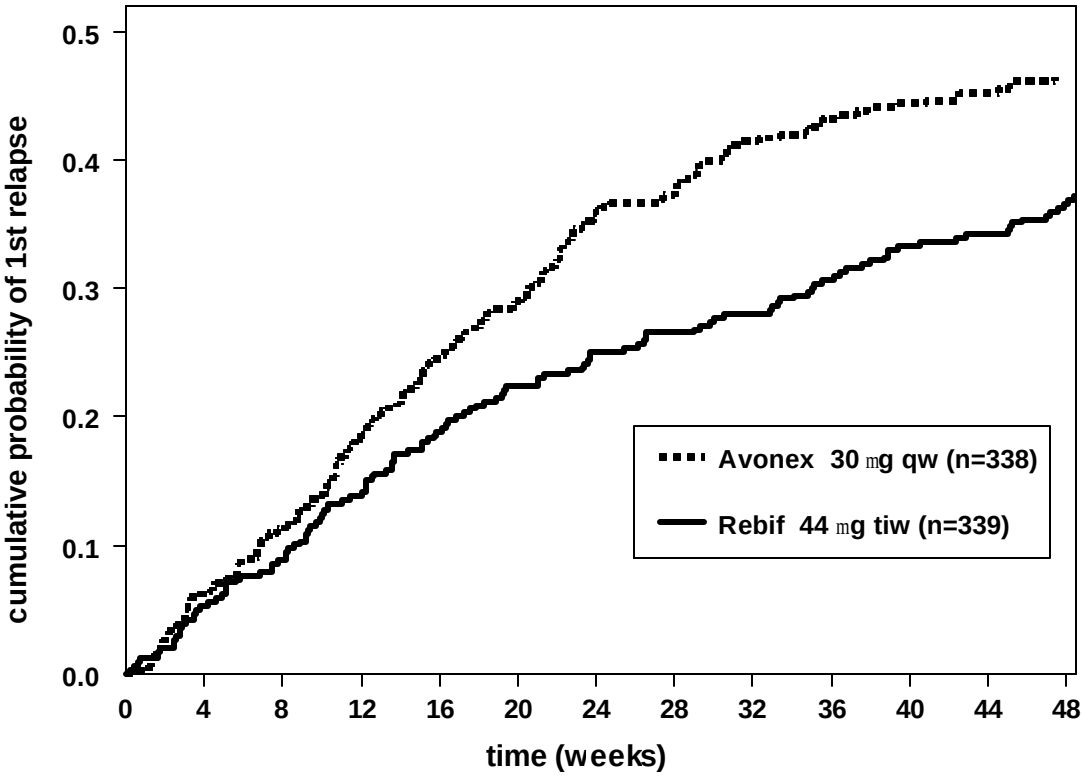
	Rebif N = 339 N (%)	**Avonex** N = 338 N (%)	Odds Ratio (95% CI) **Rebif / Avonex**	Relative Risk (95% CI) **Rebif / Avonex**
Exacerbation-Free				
24 weeks	254 (74.9)*	214 (63.3)	1.7 (1.2, 2.4)	1.18 (1.07, 1.31)
48 weeks	209 (61.7)**	177 (52.4)	1.5 (1.1, 2.1)	1.18 (1.03, 1.34)
Not Exacerbation-Free				
24 weeks	85 (25.1)*	124 (36.7)	0.58 (0.42, 0.80)	0.68 (0.54, 0.86)
48 weeks	130 (38.3)**	161 (47.6)	0.68 (0.50, 0.93)	0.81 (0.68, 0.96)

* $p < 0.001$ and ** $p = 0.009$, from a logistic regression model with effects for treatment and center

The results of the ITT analysis were confirmed for the Evaluable Population, and also demonstrated a significant difference in favor of Rebif® (relative risk = 1.22; 95% CI (1.04, 1.44); $p = 0.014$).

There was a 32% relative reduction in the proportion of Rebif® subjects who experienced relapses compared to Avonex®-treated subjects after 24 weeks of treatment, and a 19.5% relative reduction after 48 weeks of treatment. Figure 1 illustrates the cumulative proportion of subjects experiencing a relapse over time after starting interferon therapy.

Figure 1: Kaplan-Meier Estimates of the Cumulative Probability of Time to First Relapse



Subgroup Analyses on the Primary Endpoint

The primary exacerbation endpoint was analyzed by subgroup to assess the robustness and generalizability of the Rebif®-associated treatment advantage. Subgroup analyses are summarized in Table 6.

Subgroup analyses of the ITT Population controlling for age, gender, region, and baseline lesion counts (CU, T1, and T2) all support the efficacy of Rebif® over Avonex® on the primary endpoint.

Table 6: Subgroup Analyses, Proportion of Subjects with Exacerbations, 0-48 Weeks					
Subgroups	Rebif		Avonex		Relative Risk (95% CI) Rebif / Avonex
	n	Exacerbations (%)	n	Exacerbations (%)	
Overall	339	130 (38.3)	338	161 (47.6)	0.81 (0.68 - 0.96)
Age					
Age < 38 years	157	66 (42.0)	181	88 (48.6)	0.86 (0.68 - 1.10)
Age = 38 years	182	64 (35.2)	157	73 (46.5)	0.76 (0.58 - 0.98)
Gender					
Males	85	24 (28.2)	86	36 (41.9)	0.67 (0.44 - 1.03)
Females	254	106 (41.7)	252	125 (49.6)	0.84 (0.69 - 1.02)
Region					
United States	223	76 (34.1)	220	100 (45.4)	0.75 (0.59 - 0.95)
Canada	35	14 (40.0)	38	19 (50.0)	0.80 (0.48 - 1.34)
Europe	81	40 (49.4)	80	42 (52.2)	0.94 (0.69 - 1.27)
Baseline CU Lesion Count*					
CU lesions = 0	146	47 (32.2)	147	64 (43.3)	0.74 (0.44 - 1.00)
CU lesions > 0	179	79 (44.1)	178	88 (49.4)	0.89 (0.72 - 1.11)
Baseline T1 Lesion Count*					
T1 lesions = 0	186	62 (33 .3)	178	81 (45.5)	0.73 (0.57 - 0.95)
T1 lesions > 0	139	64 (46.0)	147	71 (48.3)	0.95 (0.75 - 1.22)
Baseline T2 Lesion Count*					
T2 lesions = 0	201	71 (35.3)	205	91 (44.4)	0.80 (0.62 – 1.01)
T2 lesions > 0	124	55 (44.4)	120	61 (50.8)	0.87 (0.67 - 1.14)

* For baseline MRI analyses, n = 325 for each group

CBER confirmed the analyses performed by the Applicant on the primary study endpoint, and all subset analyses are consistent with the overall study results.

Effect of Withdrawal on the Primary Endpoint

In each treatment group, 14 subjects withdrew from the study prior to 48 weeks. Ten of the 14 in each group withdrew without having had an exacerbation. Imputation for the primary endpoint, according to the prespecified analysis plan, led to 4 of these 10 subjects in each group being assigned as "not exacerbation-free." This number of subjects is unlikely to have had a significant effect on the study results.

Secondary Endpoints

Exacerbation Count per Subject

The primary outcome measure takes into consideration only the first clinical relapse. To further examine treatment effect, an assessment of total relapse (exacerbation) rate was performed. Relatively few subjects experienced more than one relapse during the 48 weeks of treatment - 40 on Rebif® and 48 on Avonex®. The exacerbation rates for Rebif®- and

Avonex®-treated subjects were 0.55 and 0.64 exacerbations/subject/48 weeks, respectively (CBER analysis). This represented a 14% relative reduction in exacerbations for Rebif® compared to Avonex® (Table 7).

Table 7: Exacerbation Count per Subject					
	0 - 24 weeks		0 - 48 weeks		p – value*
	Rebif N = 339	Avonex N = 338	Rebif N = 339	Avonex N = 337	
Mean (SD)	0.29 (0.54)	0.39 (0.55)	0.53 (0.81)	0.63 (0.78)	
Median	0	0	0	0	
Range	0, 2	0, 2	0, 4	0, 3	
Exacerbation Rate #	0.293	0.396	0.276	0.317	24 weeks: 0.022
					48 weeks: 0.092

* CBER analysis using Poisson Regression Model with effects for treatment and center
# exacerbations per 24 weeks

CBER assessed exacerbation rates using the ---------- data files provided by the Applicant. Annualized exacerbation rates were calculated for each subject as (number of exacerbations / days on study) x 365.25 days / year. Annualized exacerbation rates were also calculated in aggregate (total exacerbations / group ÷ total time on study / group) x 365.25 and were essentially identical.

Table 8: Number of subjects by Exacerbation Count, at 48 weeks			
Number of exacerbations	Rebif N = 339 n (%)	Avonex N = 337 n (%)	p-value*
0	213 (62.8)	180 (53.4)	0.089
1	86 (25.4)	109 (32.3)	
2	27 (8.0)	41 (12.2)	
3	12 (3.5)	7 (2.1)	
4	1 (0.3)	0 (0.0)	

*from a CMH test adjusted for center

The fractions of subjects with 1 and 2 relapses were lower in the Rebif® group compared to the Avonex® group (Table 8). Among subjects with 3 or 4 exacerbations, there were more Rebif®- than Avonex®-treated subjects (13 versus 7, respectively); however, the numbers of subjects in these categories were small.

Mean Number of T2 Active Lesions per Subject per Scan

T2 lesions are thought to possibly reflect permanent residual changes to the CNS following an initial inflammatory episode. Through 24 weeks, Rebif®-treated subjects had approximately one-third fewer T2 active lesions as Avonex®-treated subjects (Table 9). This treatment effect on the number of T2 active lesions was maintained through 48 weeks.

Table 9: Mean Number of T2 Active Lesions per Subject per MRI Scan				
	Rebif N = 325		Avonex N = 325	
	24 Weeks	48 Weeks	24 Weeks	48 Weeks
Mean (SD)	0.4 (1.0)	0.9 (2.7)	0.6 (1.2)	1.4 (3.1)
Median	0.0	0.0	0.2	0.5
Range	0.0, 8.5	0.0, 30.0	0.0, 10.2	0.0, 32.0
	Treatment Comparison (Rebif vs. Avonex)			
	24 Weeks		48 Weeks	
Mean Difference (SEM)*	- 0.2 (0.1)		- 0.6 (0.2)	
95% CI*	- 0.4, - 0.1		- 0.9, - 0.2	
p-value**	<0.001		<0.001	

*estimated using a parametric ANCOVA model on raw data with effects for treatment and center with the baseline number of T2 active lesions as the covariate
**from a nonparametric ANCOVA model with effects for treatment and center with the baseline number of T2 active lesions as the single covariate

Tertiary Endpoints

Proportion of Subjects with no T2 active lesions
Two hundred three subjects (62.5%) treated with Rebif® had no T2 active lesions compared to 145 subjects (44.6%) treated with Avonex® during the 48 week treatment period (RR = 1.40; 95% CI 1.21 – 1.62; p-value <0.0001).

Time to Clinical Exacerbation
Rebif® prolonged the time to the first clinical exacerbation during the 48-week treatment period compared to Avonex® (p =0.003; hazard ratio 0.70).

Rebif® did not significantly prolong the time to the second exacerbation during the 48-week treatment period compared to Avonex® (p =0.370; hazard ratio 0.82); however, the number of subjects with a second exacerbation was small (Table 8).

Exacerbation Severity
Overall, approximately two-thirds of all relapses were graded as moderate or severe, i.e. ≥ 1 EDSS point or ≥ 2 points on the KFS scale. The absolute number of relapses in each category was less in the Rebif® group than in the Avonex® group (see Table 10).

Table 10: Exacerbation Count by Severity				
	0-24 weeks		0-48 weeks	
	Rebif	Avonex	Rebif	Avonex
Total Number of Exacerbations (%)	98	132	180	212
Severity by EDSS/KFS				
Mild	27 (27.6)	40 (30.3)	52 (28.9)	66 (31.1)
Moderate	39 (39.8)	49 (37.1)	78 (43.3)	82 (38.7)
Severe	23 (23.5)	30 (22.7)	34 (18.9)	40 (18.9)
Not Available	9 (9.2)	13 (9.8)	16 (8.9)	24 (11.3)

Table 11: Worst Exacerbation per Subject, by Severity				
	0-24 weeks		0-48 weeks	
Severity by EDSS/KFS	Rebif N=339	Avonex N=338	Rebif N=339	Avonex N=338
None	254 (74.9)	214 (63.3)	209 (61.7)	177 (52.4)
Mild	20 (5.9)	31 (9.2)	32 (9.4)	35 (10.4)
Moderate	35 (10.3)	49 (14.5)	56 (16.5)	71 (21.0)
Severe	23 (6.8)	31 (9.2)	29 (8.6)	37 (10.9)
Not Available	7 (2.1)	13 (3.8)	13 (3.8)	18 (5.3)

The Applicant performed multiple assessments of relapse severity, using the ITT and Evaluable populations, and using severity by either EDSS/KFS or by ADL history. Each assessment produced a severity profile similar to the results displayed in Table 10. Rebif® administration was not associated with a change in the distribution of relapse severities. The treatment advantage of Rebif® in decreasing the number of exacerbations was consistent across all relapse severities, suggesting an overall reduction in relapses, rather than a shift to relapses of lesser or greater severity. This treatment advantage occurred during the first 24 weeks of the study, but exacerbation rates were the same thereafter.

Steroid Use

The rate of steroid use for MS exacerbations was 0.192 courses per subject during the 48 weeks in the Rebif® group and 0.263 courses per subject in the Avonex® group. Overall, 35% of relapses in the Rebif® group and 41% of relapses in the Avonex® group were treated with steroids.

Reviewer's Comment(s): The disparity in steroid courses per subject largely parallels the difference in numbers of relapses per subject. There is a slight trend towards greater steroid use per relapse in the Avonex® group. This trend may indicate a bias on the part of unblinded treating physicians, e.g., a greater willingness to administer steroids to Avonex® subjects. However any bias of the treating physicians regarding relapse severity and the need for steroids should not have been reflected in the assessment of severity by the evaluating physicians. Assessments of relapse severity were made by the evaluating physician prior to steroid treatment for the relapse; therefore, steroid administration was unlikely to influence the assessment of relapse severity. Also, steroid administration was standardized and limited

to methylprednisolone for three days, which would have been unlikely to affect the occurrence or severity of subsequent relapses.

Progression of Disability

Accumulation of disability in MS is slow relative to MRI events or relapses, and the protocol did not specify any 24-week analyses of disability. Progression of disability, defined as a 1-point increase in the EDSS, was assessed at 48 weeks. There were 43 Rebif® subjects and 49 Avonex® subjects who had progressed and maintained progression for confirmation 3 months later (log rank = 0.45). Based on a more stringent confirmation at 6 months, there were 20 Rebif® subjects and 28 Avonex® subjects who progressed (log rank = 0.22). Although the time to disability progression favored Rebif, the differences did not reach statistical significance, and no conclusions can be drawn regarding the relative efficacy of Rebif® and Avonex® on the endpoint of disability progression.

Change in EDSS Score from Baseline:

In the previous review of data from this study (STN # 103780 / 0, 1/23/2002), an exploratory analysis was performed to assess the change in EDSS score from baseline to 24 weeks. The Wilcoxon rank sum test yielded a statistically significant p-value of 0.041, favoring Rebif®. That review noted that any subjects who were experiencing an exacerbation at six months at the time of the neurologic evaluation would contaminate this analysis group. Over the full study, an analysis of the change in EDSS from baseline to 48 weeks shows no difference between the two groups (p = 0.964), using a two-way ANOVA model on ranked data with effects for treatment and center.

Neutralizing Antibody to Interferon-ß

The presence of neutralizing antibodies (NAb) was measured at 24 and at 48 weeks, but the data were not included in the previous BLA supplement reviewed by Dr. C. Rask (STN # 103780 / 0, 1/23/2002). At 24 weeks, 49 Rebif® subjects and 1 Avonex® subject had NAb at a titer =20 NU/ml[1]. At 48 weeks, data from 321 of 339 Rebif®-treated subjects and 308 of 337 Avonex®-treated subjects were available. Eighty-one Rebif® subjects and 7 Avonex® subjects had NAb at a titer =20 NU/ml. Two of the Rebif® subjects were transiently positive, with NAb present at Week 24 but not detectable at Week 48. Neutralizing antibodies, at any level, were detected in a total of 132 (39.4%) Rebif® subjects and in 17 (5.2%) Avonex® subjects.

Reviewer's comment(s): The number of antibody-positive subjects in the Avonex® group is too small for meaningful analysis of the relationship between antibody status and efficacy.

Some MS experts believe that neutralizing antibodies limit the long-term effectiveness of ß-interferons. For subjects who received Rebif®, Table 12 presents data on the primary outcome measure, the proportion of exacerbation-free subjects, by NAb status. The table includes the 335 subjects with known NAb status at 48 weeks.

[1] NU/mL is the unit used for reporting the titer of neutralizing antibodies. NU/mL is defined as (----------

Table 12: Proportion of Exacerbation-Free Subjects by NAb subgroup, Rebif subjects only, Weeks 0-48	
NAb category	**N / N (%)**
Negative	127 / 203 (62.6)
Any titer > 0	80 / 132 (60.6)
0 < titer < 20	26 / 48 (54.2)
20 = titer < 100	18 / 31 (58.1)
100 = titer < 500	22 / 30 (73.3)
Titer = 500	14 / 23 (60.9)

There is no apparent association between NAb status and the primary outcome measure.

***Reviewer comment*: A cumulative probability analysis by CBER of the time to first relapse did not reveal any difference between the antibody-positive and the antibody-negative Rebif® subjects.**

For subjects who received Rebif®, Tables 13 and 14 present data on the secondary outcome measures, exacerbation count and number of T2 active lesions, by NAb status (NAb positive = titer =20; NAb negative = titer <20) .

Table 13: Exacerbation Count per Subject by NAb Status (Rebif subjects only)		
	NAb positive	NAb negative
n	84	251
Mean (SD)	0.5 (0.8)	0.5 (0.8)
Median	0.0	0.0
Range	0, 3	0, 3

Table 14: T2 Active Lesions by NAb status[1, 2]		
Number of T2 lesions	NAb positive	NAb negative
0 – 24 weeks		
n	83	230
Mean (SD)	1.4 (4.3)	0.8 (1.8)
Median	0.0	0.0
24 – 48 weeks		
n	81	223
Mean (SD)	1.6 (4.5)	0.7 (2.8)
Median	0.0	0.0

[1] Excludes subjects with missing MRI or NAb data at 24 weeks or at 48 weeks
[2] NAb positive = titer =20; NAb negative = titer <20

The data suggest that subjects who develop neutralizing antibodies to Rebif® develop more T2 lesions than subjects who remain antibody negative. The clinical significance of this

finding is unclear, particularly in light of the data showing similar exacerbation rates in antibody-positive and antibody-negative subjects (Table 12; Table 13).

EFFICACY RESULTS – WEEKS 24 TO 48

Proportion of Exacerbation Free Subjects (Weeks 24 to 48)

For subjects who were exacerbation-free during the initial 24-week treatment period, the proportions of subjects who remained exacerbation-free in the second part of the study were virtually identical in the two treatment groups: 81.5% of subjects in the Rebif® treatment group and 81.8% of subjects in the Avonex® treatment group remained exacerbation-free (Table 15).

Table 15: Percent of Subjects with Exacerbations and Without Exacerbations, 24 - 48 weeks				
	Rebif N = 254 n (%)	Avonex N = 214 n (%)	p-value	Relative Risk (95% CI)
Exacerbation-Free	207 (81.5)	175 (81.8)	0.938	0.997 (0.915, 1.087)
Not Exacerbation-Free	47 (18.5)	39 (18.2)		

Exacerbation Count per Subject (Weeks 24 to 48)

The primary outcome measure over 48 weeks only takes into consideration the first clinical relapse. To further examine the duration of treatment effect, an assessment of total relapse (exacerbation) rate was performed, comparing the initial 24 weeks to the final 24 weeks. The estimated exacerbation rates were 0.254 exacerbations and 0.243 exacerbations per subject per 24 weeks for subjects treated with Rebif® and Avonex®, during weeks 24-48, respectively (Table 16).

Table 16: Exacerbation Count per Subject				
	0-24 weeks		24-48 weeks	
	Rebif N = 339	Avonex N = 337	Rebif N = 339	Avonex N = 337
Mean (SD)	0.29 (0.54)	0.39 (0.55)	0.24 (0.49)	0.24 (0.47)
Median	0	0	0	0
Range	0, 2	0, 2	0, 2	0, 2
Exacerbation Rate[*, #]	0.293	0.396	0.254	0.243

*CBER analysis
[#] exacerbations per 24 weeks

CBER assessed exacerbation rates using the ---------- data files provided by the Applicant. Annualized exacerbation rates were calculated for each subject as (number of exacerbations / days on study) x 365.25 days / year. Annualized exacerbation

rates were also calculated in aggregate (total exacerbations / group ÷ total time on study / group) x 365 and were essentially identical.

Between Weeks 24 and 48, the fractions of subjects who were exacerbation-free (Table 15) and the exacerbation counts (Table 16) were virtually the same in the two treatment groups. The imbalance in the fraction of subjects who were exacerbation-free observed during the first 24 study weeks and favoring Rebif® was not observed during weeks 24 – 48.

On the other hand, there was no apparent *increase* in the exacerbation count in the Rebif® treatment group relative to the Avonex® group during the second 24 weeks. Had such an increase been observed, it would have suggested that Rebif® merely delayed exacerbations from the initial 24 weeks to the final 24 weeks. Thus, Rebif was more effective than Avonex over the 48-week course of the study. This advantage of Rebif over Avonex is apparent in the initial 24 weeks and maintained, with no increase or decrease in this benefit, from 24-48 weeks.

Mean Number of T2 Active Lesions per Subject per Scan (24 – 48 Weeks)

T2 lesions are thought to possibly reflect permanent residual changes to the CNS following an initial inflammatory episode. Subjects treated with Rebif® had fewer T2 active lesions compared to those treated with Avonex® during the 48-week treatment period (Table 17).

Table 17: Mean Number of T2 Active Lesions per Subject per MRI Scan

	0-24 Weeks		24-48 Weeks	
	Rebif	Avonex	Rebif	Avonex
N	315	312	304	303
Mean (SD)	0.93 (2.69)	1.71 (3.88)	0.91 (3.37)	1.17 (2.64)
Median	0	1	0	0
Range	0, 31	0, 43	0, 29	0, 21

The difference in number of T2 active lesions between the two groups suggests a consistent advantage for Rebif® throughout the study. However, the differential effect is smaller in Weeks 24-48 than in Weeks 0-24. Also, the clinical meaningfulness of this differential is unclear.

SAFETY ANALYSES

Serious Adverse Events and Deaths

One death occurred during the 48-week study period. The subject was receiving Rebif® and was the victim of an airplane crash. He was the pilot and sole occupant of the airplane.

Forty-three serious adverse events occurred in 39 subjects: 24 events in the Rebif® group (6.2%) and 19 events in the Avonex® group (5.3%). The serious adverse events are shown in Table 18.

Table 18: Serious Adverse Events (48 Week Data)		
Body System Preferred term	Rebif (n = 339) n (%)	Avonex (n = 337) n (%)
Total	21 (6.2)	18 (5.3)
Body as a whole	6 (1.8)	6 (1.8)
Chest pain	1 (0.3)	2 (0.6)
Spontaneous Abortions	2 (0.6)	1 (0.3)
Allergic reaction	1 (0.3)	1 (0.3)
Death	1 (0.3)	0
Syncope	0	1 (0.3)
Joint Dislocation / Fall	1 (0.3)	0
Post-operative Pain	0	1 (0.3)
Gastro-intestinal Disorders	4 (1.2)	3 (0.9)
Abdominal Adhesions	0	1 (0.3)
Abdominal Pain	1 (0.3)	0
Diarrhea	0	1 (0.3)
Enteritis	1 (0.3)	0
Esophagitis	1 (0.3)	0
Oral neoplasm, benign	0	1 (0.3)
Rectal disorder	1 (0.3)	0
Psychiatric Disorders	4 (1.2)	2 (0.6)
Depression	1 (0.3)	2 (0.6)
Depression, aggravated	1 (0.3)	0
Emotional lability	1 (0.3)	0
Suicide attempt	1 (0.3)	0
Resistance Mechanism Disorders	4 (1.2)	0
Abscess	1 (0.3)	0
Viral Infection	1 (0.3)	0
Otitis media	1 (0.3)	0
Urinary Tract Infection	1 (0.3)	0
Respiratory Disorders	0	3 (0.9)
Bronchitis	0	1 (0.3)
Epiglottitis	0	1 (0.3)
Pneumonia	0	1 (0.3)
Reproductive Disorders, Female	1 (0.3)	1 (0.3)
Ovarian Cyst	1 (0.3)	0
Vaginitis	0	1 (0.3)
Cardiovascular Disorders	1 (0.3)	1 (0.3)
ECG abnormal	0	1 (0.3)
Tachycardia, supraventricular	1 (0.3)	0
Nervous System Disorders	0	1 (0.3)
MS aggravated	0	1 (0.3)
Spinal Cord Compression	0	1 (0.3)

Endocrine Disorders Goiter	1 (0.3) 1 (0.3)	0 0
Liver and Biliary Disorders Cholecystitis	1 (0.3) 1 (0.3)	0 0
Neoplasm Breast Neoplasm, malignant, female	1 (0.3) 1 (0.3)	0 0
Vision Disorders Diplopia	0 0	1 (0.3) 1 (0.3)
White Cell and RES Disorders Lymphopenia	1 (0.3) 1 (0.3)	0 0

Reviewer's Comment: The serious adverse event profile at 48 weeks does not raise any new concerns.

Severe Adverse Events

There were 89 severe adverse events in 53 subjects in the Rebif® treatment group (53/339, 15.6%), with four (death from airplane crash, aggravated depression, attempted suicide, and supraventricular tachycardia) rated as "life threatening" in four subjects. There were 100 severe adverse events in 60 subjects (60/337, 17.8%) in the Avonex® treatment group, with one (allergic reaction to gadolinium) rated as "life-threatening."

Other notable adverse events are shown in Table 19. They were selected because of concerns from the body of evidence that have arisen on the use of the ß-interferons, specifically related to generalized and local injection site reactions, psychiatric disturbances (particularly depression), hepatic dysfunction, cytopenias (particularly of leukopenias) and thyroid disorders.

Table 19: Selected Adverse Events by Severity
(Most Severe Event / Subject), Through 48 weeks

Preferred Term	Rebif (N = 339) n (%)			Avonex (N = 337) n (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Influenza-like Symptoms	104 (30.7)	44 (13.0)	2 (0.6)	110 (32.6)	56 (16.6)	10 (3.0)
Injection Site Pain	48 (14.2)	18 (5.3)	2 (0.6)	33 (9.8)	2 (0.6)	0
Depression	17 (5.0)	34 (10.0)	4 (1.2)	33 (9.8)	25 (7.4)	4 (1.2)
Insomnia	38 (11.2)	16 (4.7)	1 (0.3)	29 (8.6)	15 (4.5)	1 (0.3)
Anxiety	4 (1.2)	9 (2.7)	0	4 (1.2)	9 (2.7)	1 (0.3)
Emotional Lability	1 (0.3)	6 (1.8)	2 (0.6)	2 (0.6)	3 (0.9)	0

Depression, aggravated	0	0	2 (0.6)*	0	0	0
Suicide attempt	0	0	1 (0.3)	0	0	0
SGPT increased	22 (6.5)	14 (4.1)	3 (0.9)	9 (2.7)	6 (1.8)	1 (0.3)
SGOT increased	14 (4.1)	11 (3.2)	1 (0.3)	8 (2.4)	1 (0.3)	1 (0.3)
Hepatic Enzymes increased	9 (2.7)	5 (1.5)	2 (0.6)	3 (0.9)	2 (0.6)	3 (0.9)
Hepatocellular Damage	0	1 (0.3)	0	0	0	0
Leukopenia	14 (4.1)	8 (2.4)	0	2 (0.6)	0	0
Lymphopenia	4 (1.2)	7 (2.1)	1 (0.3)	0	0	1 (0.3)
Granulocytopenia	9 (2.7)	2 (0.6)	0	2 (0.6)	0	0
Thrombocytopenia	1 (0.3)	0	0	0	0	0
Thyroid disorder	4 (1.2)	0	1 (0.3)	0	0	0
Spontaneous Abortion	N/A	N/A	2 (0.6)	N/A	N/A	1 (0.3)
Seizure or possible seizure	0	0	0	1 (0.3)	1 (0.3)	1 (0.3)
Allergic reaction	2 (0.6)	1 (0.3)	1 (0.3)	5 (1.5)	5 (1.5)	1 (0.3)**

* Two aggravated depressions, one rated as severe and one rated as life-threatening
** Life-threatening

The incidence of thyroid disorders is increased in the Rebif® group compared to the Avonex® group, but the numbers are too small to be clearly meaningful, and severity is predominately mild. The incidence of liver function test abnormalities, injection site pain, and white blood cell abnormalities is increased in the Rebif® group compared to the Avonex group.

Over the initial 24 weeks, severe depression was reported slightly more frequently in the Avonex® group; however, over the course of 48 weeks, the incidences of depression (Table 20) and severe depression (Table 19) were similar in the two groups.

Reviewer's comment(s): As noted above, the incidence of injection site pain was higher in Rebif®-treated subjects than in Avonex-treated subjects. However, the frequency of injections was three times greater for the Rebif®-treated subjects, providing much greater opportunity for the Rebif®-treated subjects to have adverse events related to injections.

The incidence of severe influenza-like symptoms is higher in the Avonex® group than in the Rebif® group. However, the number of events is too small to provide conclusive evidence of a difference between the two products.

Total Adverse Events

Review of the overall adverse event profile for Rebif® included in this submission revealed it to be similar to that reported for Rebif® after the initial 24 weeks of this study and similar to that observed with other marketed β-interferons. It was also generally similar to the adverse events and their frequencies as reported in the current package inserts for Avonex® and Betaseron®, with only a few exceptions, discussed elsewhere. Adverse events that occurred in ≥ 5% of subjects in either the Rebif® or Avonex® treatment group in Study 21125 are shown in Table 20.

Table 20: Adverse events reported in = 5% of subjects on either treatment (48 week data)

Body System Preferred term	Rebif (N = 339) n (%)	Avonex (N = 337) n (%)
Body as a whole	261 (77.0)	272 (80.7)
Influenza-like symptoms	143 (42.2)	165 (49.0)
Headache	128 (37.8)	107 (31.8)
Fatigue	60 (17.7)	69 (20.5)
Fever	17 (5.0)	26 (7.7)
Rigors	11 (3.2)	22 (6.5)
Application site disorders	282 (83.2)	93 (27.6)
Injection site reaction	119 (35.1)	41 (12.2)
Injection site inflammation	99 (29.2)	13 (3.9)
Injections site pain	66 (19.5)	34 (10.1)
Injection site rash	52 (15.3)	5 (1.5)
Injection site bruising	27 (8.0)	12 (3.6)
Respiratory Disorders	177 (52.2)	177 (52.5)
Rhinitis	73 (21.5)	80 (23.7)
Upper Respiratory Tract Infection	55 (16.2)	59 (17.5)
Sinusitis	47 (13.9)	43 (12.8)
Pharyngitis	29 (8.6)	35 (10.4)
Bronchitis	24 (7.1)	15 (4.5)
Gastro-intestinal Disorders	125 (36.9)	125 (37.1)
Nausea	37 (10.9)	30 (8.9)
Abdominal Pain	27 (8.0)	18 (5.3)
Diarrhea	20 (5.9)	20 (5.9)
Constipation	16 (4.7)	18 (5.3)
Gastroenteritis	17 (5.0)	11 (3.3)
Dyspepsia	8 (2.4)	18 (5.3)
Nervous System Disorders	123 (36.3)	107 (31.8)
Dizziness	31 (9.1)	31 (9.2)
Hypertonia	21 (6.2)	27 (8.0)
Paraesthesia	18 (5.3)	15 (4.5)
Hypoaesthesia	19 (5.6)	7 (2.1)

Musculo-Skeletal Disorders	116 (34.2)	112 (33.2)
Myalgia	41 (12.1)	48 (14.2)
Back Pain	36 (10.6)	41 (12.2)
Arthralgia	37 (10.9)	31 (9.2)
Psychiatric Disorders	118 (34.8)	106 (31.5)
Depression	55 (16.2)	61 (18.1)
Insomnia	53 (15.6)	44 (13.1)
Resistance Mechanism Disorders	91 (26.8)	110 (32.6)
Viral Infection	37 (10.9)	43 (12.8)
Urinary Tract Infection	25 (7.4)	31 (9.2)
Infection	18 (5.3)	22 (6.5)
Liver and Biliary Disorders	60 (17.7)	32 (9.5)
SGPT Increased	39 (11.5)	16 (4.7)
SGOT Increased	26 (7.7)	10 (3.0)
White Cell and RES Disorders	38 (11.2)	16 (4.7)
Leukopenia	21 (6.2)	2 (0.6)

Abnormalities of liver function tests, decreases in white blood cell counts, and injection site reactions were more common in the Rebif® group, although most were mild to moderate in severity.

Reviewer's comment(s): As detailed in Table 20, the incidence of the adverse events is generally lower in Study 21125 than the incidence described in the label for these common adverse events in Study GF6789. The lower incidence of adverse events in the current study is probably at least partially due to the shorter study duration.

Table 21: Selected Adverse Events by Time Period

Body System Preferred term	0 - 24 weeks		0 - 48 weeks	
	Rebif (N = 339) n (%)	Avonex (N = 337) n (%)	Rebif (N = 339) n (%)	Avonex (N = 337) n (%)
Body as a whole	255 (75.2)	268 (79.5)	261 (77.0)	272 (80.7)
Influenza-like symptoms	141 (41.6)	164 (48.7)	143 (42.2)	165 (49.0)
Headache	114 (33.6)	101 (30)	128 (37.8)	107 (31.8)
Fatigue	53 (15.6)	55 (16.3)	60 (17.7)	69 (20.5)
Fever	15 (4.4)	23 (6.8)	17 (5.0)	26 (7.7)
Rigors	10 (2.9)	21 (6.2)	11 (3.2)	22 (6.5)
Application site disorders	273 (80.5)	82 (24.3)	282 (83.2)	93 (27.6)
Injection site reaction	111 (32.7)	31 (9.2)	119 (35.1)	41 (12.2)
Injection site inflammation*	146 (43.1)	15 (4.5)	151 (44.5)	18 (5.3)
Injections site pain	62 (18.3)	31 (9.2)	66 (19.5)	34 (10.1)
Injection site bruising	26 (7.7)	12 (3.6)	27 (8.0)	12 (3.6)
Psychiatric Disorders	96 (28.3)	86 (25.5)	118 (34.8)	106 (31.5)
Depression	38 (11.2)	45 (13.4)	55 (16.2)	61 (18.1)

Liver and Biliary Disorders	47 (13.9)	22 (6.5)	60 (17.7)	32 (9.5)
SGPT Increased	26 (7.7)	9 (2.7)	39 (11.5)	16 (4.7)
SGOT Increased	21 (6.2)	3 (0.9)	26 (7.7)	10 (3.0)
White Cell and RES Disorders	24 (7.1)	9 (2.7)	38 (11.2)	16 (4.7)
Leukopenia	11 (3.2)	1 (0.3)	21 (6.2)	2 (0.6)

* Includes subjects who injection site inflammation and/or rash

Reviewer's comment(s): Table 21 provides the subject frequencies of selected adverse events by study period. As expected, the incidence of psychiatric disorders, depression, liver and biliary disorders, white cell and RES disorders, and leukopenia appear to increase in one or both treatment groups with longer administration of the agent. The incidence of other adverse events (e.g., influenza-like symptoms, fever, rigors, injection site disorders) increased only minimally with doubling of the time on study.

Pregnancies

Six pregnancies were reported during this study, four in the Rebif® treatment arm, and two in the Avonex® treatment arm. Three of the pregnancies (2 in the Rebif® group, 1 in the Avonex® group) ended in spontaneous abortions; one in the Rebif® group was terminated by a therapeutic abortion, and two pregnancies (1 in the Rebif® group, 1 in the Avonex® group) were carried to term with birth of healthy, full-term infants.

FINANCIAL DISCLOSURE STATEMENTS

FDA Forms 3454 were submitted for 51 of the 56 principal investigators who participated in study 21125 certifying their absence of financial interests as defined in 21CFR54.2(a), (b) and (f).

Four principal investigators and five subinvestigators who participated in study 21125 disclosed financial arrangements with the Applicant that may represent a conflict of interest. The individuals with potential conflicts of interest were responsible for assessment of the primary endpoint for 20 subjects. This number of subjects is unlikely to have had a significant effect on the study results.

One principal investigator and 46 subinvestigators who participated in Study 21125 have not provided updated Financial Disclosure statements.

ASSESSMENT, CONCLUSIONS, and RECOMMENDATIONS

- This BLA supplement provides the final clinical study report for Study 21125, a randomized, unblinded, active treatment, comparative, multicenter study conducted in 677 subjects with relapsing-remitting MS that utilized blinded evaluators for both the neurologic examinations and for interpretation of the MRI findings. The study was designed to compare the efficacy and safety of 44 µg of Rebif® administered SC 3 x per week *vs.* 30 µg Avonex® administered IM once weekly in delaying or preventing the occurrence of clinical exacerbations in subjects who had experienced at least two clinical exacerbations during the previous two years.

- The BLA supplement includes complete detailed safety and efficacy data from Study 21125 (the comparative study) through Week 48, previously received in summary form. CBER's analyses of the final Clinical Study Report and detailed analyses of the datasets are consistent with analyses of the study data submitted prior to approval (http://www.fda.gov/cber/review/ifnbser030702r1.pdf).

- The primary endpoint, the proportion of subjects who were exacerbation-free following 48 weeks of treatment, demonstrated Rebif® 44 µg administered SC 3 x per week to be superior to Avonex® 30 µg administered IM 1 x per week (p=0.009, relative risk of being exacerbation-free of 1.18, with a 95% confidence interval of 1.03 - 1.34). Following 48 weeks of treatment, 209 of 339 subjects (61.7%) in the Rebif® treatment group were exacerbation-free, compared with 177 of 338 subjects (52.4%) in the Avonex® treatment group. CBER confirmed the analyses performed by the Applicant.

  The data were robust to subgroup analyses of the primary endpoint. Evaluations of secondary endpoints support the overall benefit of Rebif® compared to Avonex®.

- Progression of disability was evaluated as a secondary endpoint. Overall, there were few subjects with confirmed progression of disability, which is expected given the limited study duration. Rates of disability progression were statistically indistinguishable over the 48 weeks of the study, 13% and 15% in the Rebif® and Avonex® groups, respectively.

- Neutralizing antibodies were detected in 84 of 335 (25.1%) of Rebif® subjects and in 7 of 330 (2.1%) of Avonex® subjects. The presence of neutralizing antibodies did not have any apparent effect on clinical efficacy, but was associated with an increased number of T2 lesions on MRI. The clinical significance of NAb to Rebif® and of MRI findings in MS remain uncertain.

- The observed safety profile for Rebif® was similar to the safety profile observed for Avonex®, with the exceptions of increased frequency of liver function test abnormalities, decreases in white blood cell counts and injection site reactions that were generally mild to moderate in severity. These adverse events have been observed to occur at similar rates in other studies of Rebif® administered subcutaneously and are common to all the interferon-betas.

Conclusions:

This study should be viewed as demonstrating that the treatment advantage of Rebif® over Avonex® in reducing the frequency of clinical exacerbations in subjects with relapsing-remitting MS, previously observed at 24 weeks, is confirmed at 48 weeks. Importantly, however, during Weeks 24-48, the frequency of relapses was similar in the two treatment groups. The only advantage of Rebif® over Avonex® during Weeks 24 – 48 was residual

from that provided during Weeks 0 – 24. The longer duration of treatment does not result in any increase or any decrease in the differential in efficacy between Rebif® and Avonex®.

This study does not support any conclusion regarding effects on the accumulation of physical disability.

This study demonstrates that neutralizing antibodies commonly occur in MS subjects who receive Rebif®. Although the development of NAb was associated with increasing T2 lesions on MRI, there was no apparent effect on clinical efficacy. The clinical meaningfulness of the development of NAb to Rebif® remains uncertain.

The adverse event profile during weeks 24 to 48 was consistent with that observed in the initial 24 weeks of study – and in previous studies, and does not raise any new safety concerns. This study also confirms that Rebif® is associated with more frequent abnormalities of liver function tests, cytopenias, and injection site reactions than Avonex®.

Recommendations:

The clinical studies section of the product label should be revised to reflect the full 48 weeks of data from Study 21125.

REFERENCES

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